Curtailed short-term and long-term survival following infection with non-typhoid *Salmonella* in Israel

M. Weinberger[1,2], S. Yaron[3], V. Agmon[4], R. Yishai[4,*], A. Rosenberg[5] and C. Peretz[5]

1) *Infectious Diseases Unit, Assaf Harofeh Medical Center, Zerifin,* 2) *The Sackler School of Medicine, Tel Aviv University, Tel Aviv,* 3) *Faculty of Biotechnology and Food Engineering, Technion, Israel Institute of Technology, Haifa,* 4) *Government Central Laboratories, Ministry of Health, Jerusalem and* 5) *School of Public Health, Epidemiology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

Abstract

Among bacterial foodborne pathogens, non-typhoid *Salmonella enterica* (NTS) is a leading cause of death worldwide. This study assessed short-term and long-term mortality following NTS infection in Israel, and evaluated the effects of age, sex, source of isolation and different serotypes on mortality. The source of data was a national registry of NTS isolates submitted to the *Salmonella* Reference Center, Government Central Laboratories, in Jerusalem, Israel, during 1997–2006. Vital status was derived from the registry of the Israeli Ministry of the Interior. The survival of a cohort of 15 919 patients infected with the top five NTS serotypes was evaluated by calculating age-standardized mortality ratios (SMRs) and by Cox proportional hazards multivariate regressions at three follow-up time intervals: 30 days, 1 year and end of follow-up. The median follow-up time was 6.44 years (mean, 6.21 years; range, 1 day to 10.80 years). The cumulative crude mortality rates at the three time intervals were 0.68%, 1.86% and 4.40%, respectively, corresponding to increased SMRs of 16.95 (95% CI 13.9–20.46), 4.25 (95% CI 3.78–4.76), and 1.83 (95% CI 1.70–1.97), respectively. Cox regressions revealed that increasing age, extraintestinal source of isolation and NTS serotype had significant effects on mortality within all three follow-up intervals. The risk of mortality was increased for serotypes Infantis and Typhimurium, and decreased for serotypes Virchow and Hadar, as compared with serotype Enteritidis. The study revealed curtailed short-term and long-term survival following NTS infection that persisted for many years following detection by culture.

Keywords: Bacteraemia/mortality, Israel/epidemiology, multivariate analysis, *Salmonella* infections/epidemiology, survival
Original Submission: 13 December 2009; **Revised Submission:** 19 January 2010; **Accepted:** 21 January 2010
Editor: G. Pappas
Article published online: 2 February 2010
Clin Microbiol Infect 2011; **17:** 278–284
10.1111/j.1469-0691.2010.03184.x

Corresponding author: M. Weinberger, Infectious Diseases Unit, Assaf Harofeh Medical Center, Zerifin 70300, Israel
E-mail: miriw@netvision.net.il

*Present address: Department of Laboratories, Ministry of Health, Jerusalem, Israel.

Introduction

Non-typhoid *Salmonella enterica* (NTS) is a predominant cause of foodborne illnesses worldwide. The majority of cases present as self-limited gastroenteritis; however, up to 8% of these illnesses may be invasive, and present as bacteraemia or other forms of extraintestinal infection [1]. Death occurs in <1% of infected patients; however, as *Salmonella* illnesses are common, the impact on public health is considerable [2–5]. In the USA and the UK, salmonellae are leading causes of death among patients with foodborne bacterial infections [2,3].

The well-defined risk factors for adverse outcome include patient age [6–10], presence of underlying disease, particularly defects in cellular immunity [5,8,10,11], and the presence of bacteraemia or other invasive disease [7,12]. Infection by a drug-resistant *Salmonella* strain has also been associated with increased mortality [13]. Less is known about long-term survival following NTS infection. Studies from Denmark have shown that mortality at 1 year is 2.9-fold higher than that of the general population, after adjustment for underlying illnesses [14].

In Israel, NTS illnesses constitute an important challenge to health authorities [15]. This is because of the high incidence of NTS in Israel, which was of the order of 50 per 100 000 population in 2003 [15], as compared with 13.4 per 100 000 in the USA [4] and 31.1 per 100 000 in the Euro-

pean Union [16]. Another important and unique trend in Israel is the predominance of serotype Virchow, which emerged in the late 1980s, and during the study years has become the second most prevalent serotype, accounting for 15–16% of all stool isolates and 22–27% of all blood isolates [15,17,18]. However, except for selected case series, mortality due to salmonellosis has not been studied in this country [10,19]. The aim of the study was to assess the impact of NTS illnesses on patient survival using a large national database of laboratory-confirmed cases.

Materials and Methods

Source of data: *Salmonella* registry

Salmonellosis is a reportable disease in Israel. Cases of salmonellosis submitted to the *Salmonella* Reference Center, Government Central Laboratories, Israel Ministry of Health, Jerusalem, between 1 January 1997 and 31 December 2006, formed the source population for the study. Human *Salmonella* isolates from all sources are submitted passively by all clinical microbiology laboratories around the country to the *Salmonella* Reference Center, where final serological identification has been performed according to the Kauffmann–White scheme for the last 60 years [20]. A patient's record includes: name, ID number, age, the date and source of *Salmonella* isolation and the identified serotype name.

Study cohort and vital status determination

During the years 1997–2006, the *Salmonella* Reference Center confirmed *Salmonella* species and performed serotype identification for 40 018 submitted patient isolates. ID numbers were available for 32 399 patients. Patient ID and demographic data were matched with the registry of the Israeli Ministry of the Interior to retrieve the exact date of birth, sex and vital status by 18 October 2007. For patients who died, the date of death was provided.

A match could be verified for 25 975 patients. The reasons for match failure were incomplete or incorrect entry of ID number or patient name. Patients with more than one isolate (with the same serotype) within 12 months were counted only once, using the earliest date of isolation. Patients with relapse of salmonellosis beyond 12 months and those who were infected with more than one NTS serotype were excluded. The sources of *Salmonella* isolation were categorized into stool and extraintestinal sources (all sources that were not stool). Patients who had *Salmonella* isolated from both stool and an extraintestinal source were counted only once and categorized as having an extraintestinal source. The earliest date of isolation was used.

After exclusion of patients with relapse and patients with multiple *Salmonella* serotypes, there remained 23 138 cases of salmonellosis caused by 180 different NTS serotypes. Five serotypes, Enteritidis, Virchow, Typhimurium, Hadar and Infantis, were responsible for 69% of the illnesses (15 919 cases) and for 73% of death events (700). The 15 919 patients with NTS infection caused by the top five serotypes were included in the study cohort and were followed for vital status from the time of culture positivity until death or 18 October 2007, whichever occurred first.

Statistical analysis

Three follow-up endpoints were selected to assess short-term and long-term survival intervals: 30 days, 1 year and end of follow-up time. The data were analysed in three steps. In the first step, the overall and sex-specific, age-standardized mortality ratios (SMRs) were calculated using the PAMCOMP program [21], to compare mortality in the studied population and that in the general Israeli population. Person-months at risk were calculated from the reported onset of the disease until either death or 18 October 2007, whichever occurred first. SMRs were calculated by dividing the observed number of deaths by the number of expected deaths in the general population. The expected deaths were calculated by multiplying person-months at risk by the national death rates, for the same age and sex categories in the years 2000–2001 (study period average) derived from the Israeli Bureau of Statistics (which can be accessed at http://www1.cbs.gov.il/reader/shnatonenew_site.htm). Analyses were repeated for all three follow-up endpoints. In the second step, Kaplan–Meier survival curves were constructed to compare mortality between patients with different categories of age, sex, source of NTS isolation and NTS serotypes. In the third step, Cox proportional hazards multivariate regressions were constructed for the estimation of the hazard ratios (HRs) of age, sex, source of NTS isolation and NTS serotype associated with mortality. Analyses were repeated for all three follow-up intervals. SPSS version 16 (SPSS Inc., Chicago, Il, USA) was used for the analyses. All p-values are two-sided.

Ethics considerations

The study was approved by the local Ethics Committee of the Assaf Harofeh Medical Center, Zerifin, Israel. Special permission for patient data matching for vital status was granted by the Ministry of Health legal counsellor. For purposes of confidentiality, after the match, each patient was given a unique number, and the actual name and ID number were erased.

Results

The study cohort included 8269 males and 7650 females, with a median age of 3.06 years (mean, 15.47 ± 23.05 years; range, 1 day to 104 years). The median patient follow-up time was 6.44 years (mean, 6.21 ± 2.70 years; range, 1 day to 3942 days or 10.80 years).

Relative mortality in comparison with the general population

One hundred and nine (0.68%) patients died within 30 days, 297 (1.86%) within 1 year, and 700 (4.40%) by the end of the follow-up time. After exclusion of four patients who were older than 100 years, comparison with the general population yielded highly significant increased age-adjusted mortality, for the whole group as well as for each sex, within the time to follow-up endpoints in all cases (Table 1). SMRs were highest within 30 days following NTS isolation and lowest by the end of the follow-up time. For the whole cohort, the SMRs decreased from 16.95 (95% CI 13.91–20.46) within 30 days, to 4.25 (95% CI 3.78–4.76) within 1 year, to 1.83 (95% CI 1.70–1.97) by the end of the follow-up time.

Kaplan–Meier survival estimates.

Figure 1 presents Kaplan–Meier survival curves extending to the end of the follow-up period for different categories of age (Fig. 1a), sex (Fig. 1b), source of NTS isolation (Fig. 1c) and NTS serotype (Fig. 1d). The log-rank tests yielded significant effects of age ($p < 0.001$) and source of NTS isolation ($p < 0.001$), and non-significant effects of sex (p 0.14) and NTS serotype (p 0.57).

Effects of age, sex, source of isolation and serotypes

Table 2 presents the adjusted HRs of age, sex, source of NTS isolation (extraintestinal vs. stool) and NTS serotypes on mortality within the three follow-up intervals. The adjusted HRs of age for mortality were highly significant ($p < 0.001$). Patients who were 75 years and older had the highest risk within all three follow-up intervals (Table 2). For each age group, the adjusted HRs for mortality increased with increasing follow-up time. For example, the adjusted HRs in patients 75 years or older as compared with patients younger than 20 years increased from 81.31 (95% CI 33.80–195.59) within 30 days, to 137.00 (95% CI 79.42–236.32) within 1 year, to 282.51 (95% CI 194.33–410.69) by the end of the follow-up time (Table 2). The only difference among sexes was found at the end of the follow-up time after adjustment for the other variables; males had a slightly higher adjusted risk than females (HR 1.19, 95% CI 1.03–1.39, p 0.02) (Table 2).

TABLE 1. Standardized mortality ratios (SMRs) and 95% CIs for *Salmonella* illnesses stratified by sex at three follow-up endpoints, Israel 1997–2006

Follow-up intervals	Observed deaths	Expected deaths	SMRs (95% CI)
Thirty days			
Males	58	3.38	17.14 (13.02–22.16)
Females	50	3.01	16.59 (12.32–12.88)
All	108	6.37	16.95 (13.91–20.46)
One year			
Males	152	36.38	4.18 (3.54–4.90)
Females	143	33.23	4.30 (3.63–5.07)
All	295	69.43	4.25 (3.78–4.76)
End of follow-up			
Males	354	192.03	1.84 (1.66–2.05)
Females	342	187.69	1.82 (1.63–2.03)
All	696	379.66	1.83 (1.70–1.97)

Note: SMRs, standardized mortality ratios analyses.

NTS was isolated from extraintestinal sources in 3.3% of the whole study cohort, and in 3.5%, 4.5%, 3.0%, 1.7% and 2.4%, respectively, of patients with serotypes Enteritidis, Virchow, Typhimurium, Hadar and Infantis. The adjusted HRs of the NTS source for mortality were significant ($p < 0.001$) within all three follow-up intervals. Patients with an extraintestinal source of *Salmonella* had significantly higher HRs than those in whom stool was the only source (Table 2). Adjusted HRs for mortality decreased by approximately 50% with increasing follow-up time intervals, from 12.12 (95% CI 7.86–18.71) within 30 days, to 6.23 (95% CI 4.86–8.00) within 1 year, to 3.76 (95% CI 3.16–4.48) by the end of the follow-up time.

The adjusted HRs of the NTS serotype for mortality were significant at the three follow-up intervals (Table 2). There was an increased mortality risk with serotypes Infantis and Typhimurium, and a decreased mortality risk with serotypes Virchow and Hadar, as compared with serotype Enteritidis.

Discussion

The study revealed that patients with NTS infection due to the most frequent serotypes in Israel, i.e. Enteritidis, Virchow, Typhimurium, Hadar and Infantis, had curtailed short-term and long-term survival as compared with the general Israeli population. These findings were based on data from a large laboratory-based national database, collected over a 10-year period (1997–2006), with a follow-up time of up to 10.8 years (mean, 6.2 years). Excess mortality as indicated by SMRs was highest at 30 days following NTS detection in culture (16.95), but remained significant at 1 year (4.25) and at the end of the follow-up period (1.83).

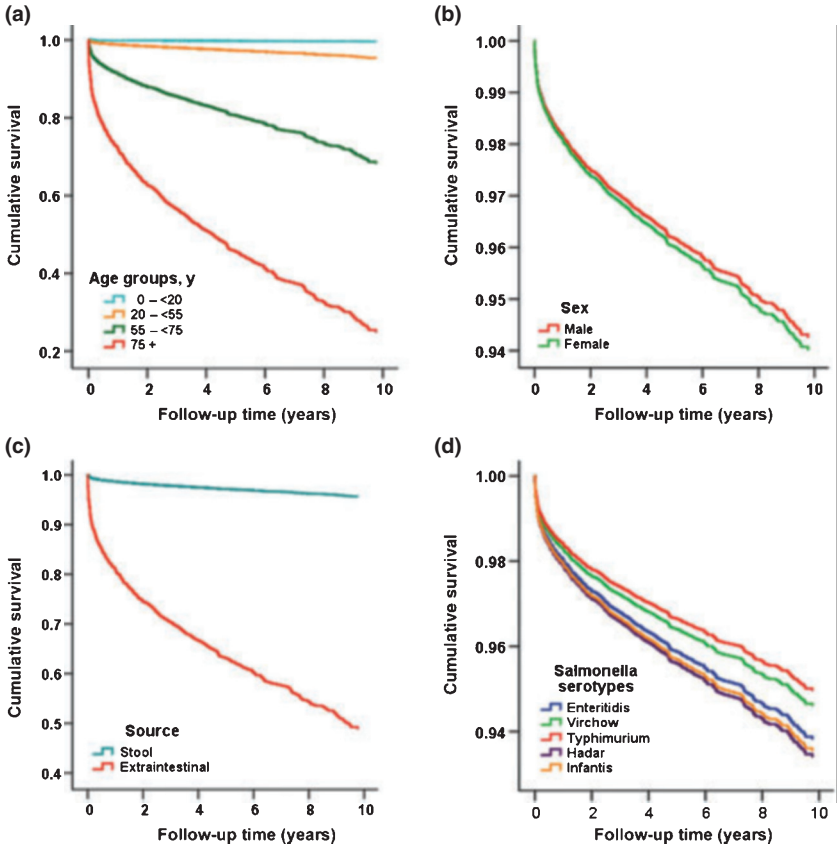

FIG. 1. Kaplan–Meier survival curves for different categories of age groups (a), sex (b), *Salmonella* isolation source (c) and *Salmonella* serotypes (d) for 15 919 patients with *Salmonella* illnesses, Israel 1997–2006. The patients were followed from 1 January 1997 until 18 October 2007, giving a total of 10.8 years. The results of log-rank tests were as follows: p <0.001 for differences between the age groups, p 0.14 for the differences between the two sex categories, p <0.001 for the differences between the two source categories, and p 0.57 for the overall differences between the serotype categories.

A comparable trend for 30-day and 1-year intervals was found in two other studies [9,14]. In the first, a large population-based study from Denmark [14], crude SMRs at 30 days and at 1 year were 15.4 and 3.4, respectively. In the second study from Sweden, corresponding SMRs were 5.6 and 1.8, respectively, for patients with domestically acquired NTS [9].

The present study evaluated the effect of age, sex, source of NTS and *Salmonella* serotypes on mortality risk. Except for sex, all of these variables had an impact on both short-term and long-term mortality up to 10.8 years of follow-up. Male sex was associated with an increased risk of mortality only at the end of the follow-up period, and this may reflect the decreased life-expectancy of males in the general population. The effect of age increased with increasing follow-up time intervals, whereas the effect of the NTS source was maximal within 30 days, and decreased over time.

Other studies have pointed to the important effect of age on short-term mortality in patients with NTS infections. A population-based FoodNet active surveillance study concerning the years 1997–1999 [5] indicated an overall case-fatality rate of 0.6%, which increased to 3.5% among the elderly (≥60 years). The case-fatality rate was 74-fold higher in the elderly than in patients <20 years, and eight-fold higher than in patients aged 20 to <60 years. In a similar epidemiological study from California [6], the mortality rates in patients aged ≥80 years (6.4%) were 92-fold higher than in patients aged <17 years and 2.7-fold higher than in patients aged 65–79 years.

A more recent FoodNet study [12] concerning the period 1996–2006 reported an acute mortality rate of 3.3% in patients with invasive disease, as compared with 0.2% in patients with enteric infection and 0.5% in the entire group.

The impact of invasive NTS infection beyond 30 days was reported in a single Danish study [22]. At 1 year of follow-up, the mortality rate in hospitalized patients with NTS bacteraemia was 21.1%, as compared with 8.1% in patients hospitalized because of NTS without bacteraemia and 0.2% in non-hospitalized patients with NTS.

Another notable finding in the present study consisted in the different effects of the specific *Salmonella* serotypes on mortality. Interestingly, serotype Virchow, with the highest proportion of extraintestinal isolation, was associated with lower rates of mortality than serotype Enteritidis during all time intervals. One possible explanation is that there are differences in age-related invasiveness [23]. In a previous study from Israel, serotype Virchow was the most invasive NTS

TABLE 2. Cox proportional hazards regression models for the effects of age, sex, source of *Salmonella* isolation and *Salmonella* serotype on mortality at three follow-up endpoints; multivariate analyses, Israel 1997–2006

Categories	Cumulative no. of deaths (%)	p-value	Adjusted HR (95% CI)
30-day interval			
Age group (years)	–	<0.001	–
0 to <20 (*n* = 11781)[a]	6 (0.051)	–	1.00
20 to <55 (*n* = 2477)	12 (0.48)	<0.001	8.27 (3.09–22.11)
55 to <75 (*n* = 1071)	29 (2.71)	<0.001	30.97 (12.62–76.02)
≥75 (*n* = 590)	62 (10.51)	<0.001	81.31 (33.80–195.59)
Sex			
Female (*n* = 7650)[a]	59 (0.65)	–	1.00
Male (*n* = 8269)	50 (0.71)	0.52	1.13 (0.78–1.66)
Source			
Stool (*n* = 15392)[a]	41 (0.27)	–	1.00
Extraintestinal (*n* = 527)	68 (12.90)	<0.001	12.12 (7.86–18.71)
Salmonella serotype	–	0.01	–
Enteritidis (*n* = 6146)[a]	52 (0.85)	–	1.00
Virchow (*n* = 3524)	13 (0.37)	0.19	0.66 (0.36–1.22)
Typhimurium (*n* = 3080)	24 (0.78)	0.25	1.33 (0.82–2.16)
Hadar (*n* = 2222)	9 (0.41)	0.34	0.71 (0.34–1.45)
Infantis (*n* = 947)	11 (1.16)	0.01	2.34 (1.21–4.54)
One-year interval			
Age group (years)	–	<0.001	–
0 to <20 (*n* = 11781)[a]	15 (0.13)	–	1.00
20 to <55 (*n* = 2477)	38 (1.53)	<0.001	11.63 (6.39–21.16)
55 to <75 (*n* = 1071)	96 (8.96)	<0.001	56.23 (32.45–97.45)
≥75 (*n* = 590)	148 (25.08)	<0.001	137.00 (79.42–236.32)
Sex			
Female (*n* = 7650)[a]	143 (1.87)	–	1.00
Male (*n* = 8269)	154 (1.86)	0.28	1.13 (0.90–1.43)
Source			
Stool (*n* = 15392)[a]	168 (1.09)	–	1.00
Extraintestinal (*n* = 527)	129 (24.48)	<0.001	6.23 (4.86–8.00)
Salmonella serotype	–	0.02	–
Enteritidis (*n* = 6146)[a]	130 (2.12)	–	1.00
Virchow (*n* = 3524)	53 (1.50)	0.43	0.88 (0.64–1.21)
Typhimurium (*n* = 3080)	62 (2.01)	0.05	1.35 (0.99–1.82)
Hadar (*n* = 2222)	32 (1.44)	0.14	0.74 (0.50–1.10)
Infantis (*n* = 947)	20 (2.11)	0.12	1.46 (0.91–2.35)
End of follow-up interval			
Age group (years)	–	<0.001	–
0 to <20 (*n* = 11781)[a]	31 (0.26)	–	1.00
20 to <55 (*n* = 2477)	80 (3.23)	<0.001	12.23 (8.07–18.53)
55 to <75 (*n* = 1071)	240 (22.41)	<0.001	88.86 (61.00–129.44)
≥75 (*n* = 590)	349 (59.15)	<0.001	282.51 (194.33–410.69)
Sex			
Female (*n* = 7650)[a]	344 (4.50)	–	1.00
Male (*n* = 8269)	356 (4.31)	0.02	1.19 (1.03–1.39)
Source			
Stool (*n* = 15392)[a]	498 (3.24)	–	1.00
Extraintestinal (*n* = 527)	202 (38.33)	<0.001	3.76 (3.16–4.48)
Salmonella serotype	–	0.02	–
Enteritidis (*n* = 6146)[a]	277 (4.51)	–	1.00
Virchow (*n* = 3524)	135 (3.83)	0.24	0.88 (0.72–1.09)
Typhimurium (*n* = 3080)	124 (4.03)	0.08	1.21 (0.98–1.49)
Hadar (*n* = 2222)	116 (5.22)	0.83	0.98 (0.78–1.21)
Infantis (*n* = 947)	48 (5.07)	0.03	1.40 (1.03–1.91)

HR, hazard ratio.
[a]Reference category.

serotype in young children, but serotypes Enteritidis and Typhimurium were more invasive in the elderly, who also have the highest risk of mortality [23]. A recently published FoodNet-based study [12] also highlighted the variability in mortality rates in patients infected with the different NTS serotypes.

Long-term effects of serotypes on mortality were reported in two studies from Denmark [8,14]. One-year mortality rates in patients with the two predominant serotypes, Enteritidis and Typhimurium, were slightly higher than in patients with other 'exotic' serotypes, and substantially lower than in patients with serotype Dublin. The reasons for the long-term consequences of NTS infection is not clear.

Possible explanations include the tendency of *Salmonella* to invade, and establish infection in more vulnerable hosts and the direct effect of infection on the host. NTS infection may result in late relapses and complications, including endocarditis, endovascular infection, osteomyelitis and bowel perforation, all of which may significantly curtail survival [1,14,24]. Acute NTS infection may also augment its impact by worsening the underlying illnesses, similar to the effects of influenza [25]. Furthermore, as many as 22.8% of the patients with documented salmonellosis in the USA required

hospitalization [12], with the potential of being exposed to nosocomial infections and iatrogenic events [26]. These findings may not be unique to NTS. Decreased survival rates at long-term follow-up were also reported in hospitalized patients with bacteraemia, West Nile encephalitis and severe sepsis [27–29].

The strength of the present study lies in the large cohort of patients with NTS infection derived from a national database, the long follow-up time and the strong validation of infection (laboratory confirmation) and death events (national registry). The unique epidemiology in Israel enabled us to study the effects of five different NTS serotypes on mortality. Long-term mortality associated with serotypes Virchow, Hadar and Infantis has not been previously reported.

The main limitation of the study lies in the lack of information regarding two confounders: patient comorbidities [14] and drug resistance [14,30]. In a study from Denmark [14], crude and comorbidity-adjusted relative mortality risks in patients with NTS, as compared with the general population, differed by approximately 20%. Notably, in the Danish study, 94% of the 26 974 patients with NTS infection had no comorbidities.

Another limitation of the present study derives from a dropout rate of approximately one-third of the patients registered in the Salmonella Reference Laboratory, owing to faulty IDs. However, this is assumed to be a random occurrence. Additionally, the low fatality rate of NTS disease might lead to less precise estimations of mortality risks.

The significant effect of NTS illnesses on long-term survival found in this study adds to the substantial burden of acute infection on the public health. Curtailed short-term and long-term survival associated with NTS infection emphasizes the need for more effective intervention to guarantee the safety of our food chain.

Acknowledgements

The authors wish to thank the team at the Israeli *Salmonella* Reference Center for their work over the years with regard to the identification and further characterization of bacterial strains, which made the writing of this article possible. Their work is highly respected and appreciated.

Transparency Declaration

This research was supported by grant no. 1275/04 from the Israel Science Foundation. The authors have no conflict of interest regarding this article.

References

1. Pegues DA, Miller SI. *Salmonella* species, including *Salmonella* Typhi. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*, 6th edn. Philadelphia, PA: Churchill Livingstone, Elsevier, 2009;2887–2903.
2. Mead PS, Slutsker L, Dietz V *et al.* Food-related illness and death in the United States. *Emerg Infect Dis* 1999; 5: 607–625.
3. Adak GK, Long SM, O'Brien SJ. Trends in indigenous foodborne disease and deaths, England and Wales: 1992 to 2000. *Gut* 2002; 51: 832–841.
4. Voetsch AC, Van Gilder TJ, Angulo FJ *et al.* FoodNet estimate of the burden of illness caused by nontyphoidal Salmonella infections in the United States. *Clin Infect Dis* 2004; 38 (suppl 3): S127–S134.
5. Kennedy M, Villar R, Vugia DJ *et al.* Hospitalizations and deaths due to Salmonella infections, FoodNet, 1996–1999. *Clin Infect Dis* 2004; 38 (suppl 3): S142–S148.
6. Trevejo RT, Courtney JG, Starr M, Vugia DJ. Epidemiology of salmonellosis in California, 1990–1999: morbidity, mortality, and hospitalization costs. *Am J Epidemiol* 2003; 157: 48–57.
7. Vugia DJ, Samuel M, Farley MM *et al.* Invasive Salmonella infections in the United States, FoodNet, 1996–1999: incidence, serotype distribution, and outcome. *Clin Infect Dis* 2004; 38 (suppl 3): S149–S156.
8. Gradel KO, Schonheyder HC, Pedersen L, Thomsen RW, Norgaard M, Nielsen H. Incidence and prognosis of non-typhoid Salmonella bacteraemia in Denmark: a 10-year county-based follow-up study. *Eur J Clin Microbiol Infect Dis* 2006; 25: 151–158.
9. Ternhag A, Torner A, Ekdahl K, Giesecke J. Salmonella-associated deaths, Sweden, 1997–2003. *Emerg Infect Dis* 2006; 12: 337–339.
10. Shimoni Z, Pitlik S, Leibovici L *et al.* Nontyphoid Salmonella bacteremia: age-related differences in clinical presentation, bacteriology, and outcome. *Clin Infect Dis* 1999; 28: 822–827.
11. Levine WC, Buehler JW, Bean NH, Tauxe RV. Epidemiology of nontyphoidal Salmonella bacteremia during the human immunodeficiency virus epidemic. *J Infect Dis* 1991; 164: 81–87.
12. Jones TF, Ingram LA, Cieslak PR *et al.* Salmonellosis outcomes differ substantially by serotype. *J Infect Dis* 2008; 198: 109–114.
13. Helms M, Simonsen J, Molbak K. Quinolone resistance is associated with increased risk of invasive illness or death during infection with Salmonella serotype Typhimurium. *J Infect Dis* 2004; 190: 1652–1654.
14. Helms M, Vastrup P, Gerner-Smidt P, Molbak K. Short and long term mortality associated with foodborne bacterial gastrointestinal infections: registry based study. *BMJ* 2003; 326: 357–360.
15. Weinberger M, Keller N. Recent trends in the epidemiology of nontyphoid Salmonella and antimicrobial resistance: the Israeli experience and worldwide review. *Curr Opin Infect Dis* 2005; 18: 513–521.
16. European Food Safety Authority, European Centre for Disease Prevention and Control. The Community summary report on trends and sources of zoonoses and zoonotic agents in the European Union in 2007. *EFSA J* 2009;223:1–312.
17. Weinberger M, Solnik-Isaac H, Shachar D *et al.* Salmonella enterica serotype Virchow: epidemiology, resistance patterns and molecular characterisation of an invasive Salmonella serotype in Israel. *Clin Microbiol Infect* 2006; 12: 999–1005.
18. Solnik-Isaac H, Weinberger M, Tabak M, Ben-David A, Shachar D, Yaron S. Quinolone resistance of Salmonella enterica serovar Virchow isolates from humans and poultry in Israel: evidence for clonal expansion. *J Clin Microbiol* 2007; 45: 2575–2579.
19. Bar-Meir M, Raveh D, Yinnon AM, Benenson S, Rudensky B, Schlesinger Y. Non-Typhi Salmonella gastroenteritis in children presenting to the emergency department: characteristics of patients with associated bacteraemia. *Clin Microbiol Infect* 2005; 11: 651–655.

20. Kauffmann F. *Classification of bacteria. A realistic scheme with special reference to the classification of Salmonella and Escherichia species*. Copenhagen: Munksgaard, 1975.
21. Taeger D, Sun Y, Keil U, Straif K. A stand-alone windows applications for computing exact person-years, standardized mortality ratios and confidence intervals in epidemiological studies. *Epidemiology* 2000; 11: 607–608.
22. Gradel KO, Schonheyder HC, Lundbye-Christensen S, Ejlertsen T, Nielsen H. Severity of human non-typhoid salmonellosis as a predictor of short- and long-term mortality. *Scand J Infect Dis* 2009; 41: 99–104.
23. Weinberger M, Andorn N, Agmon V, Cohen D, Shohat T, Pitlik SD. Blood invasiveness of *Salmonella enterica* as a function of age and serotype. *Epidemiol Infect* 2004; 132: 1023–1028.
24. Cohen JI, Bartlett JA, Corey GR. Extra-intestinal manifestations of *Salmonella* infections. *Medicine* 1987; 66: 349–388.
25. Treanor JJ. Influenza virus. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*, 5th edn. Philadelphia, PA: Elsevier, Churchill Livingstone, 2005; 2060–2085.
26. Baker GR, Norton PG, Flintoft V *et al.* The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ* 2004; 170: 1678–1686.
27. Leibovici L, Samra Z, Konigsberger H, Drucker M, Ashkenazi S, Pitlik SD. Long-term survival following bacteremia or fungemia. *JAMA* 1995; 274: 807–812.
28. Green MS, Weinberger M, Ben-Ezer J *et al.* Long-term death rates, West Nile virus epidemic, Israel, 2000. *Emerg Infect Dis* 2005; 11: 1754–1757.
29. Laupland KB, Zygun DA, Doig CJ, Bagshaw SM, Svenson LW, Fick GH. One-year mortality of bloodstream infection-associated sepsis and septic shock among patients presenting to a regional critical care system. *Intensive Care Med* 2005; 31: 213–219.
30. Helms M, Vastrup P, Gerner-Smidt P, Molbak K. Excess mortality associated with antimicrobial drug-resistant Salmonella typhimurium. *Emerg Infect Dis* 2002; 8: 490–495.